Enhanced Suppression of Cortisol Following Dexamethasone Administration in Posttraumatic Stress Disorder

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Objective: *The authors investigated the possibility of enhanced negative feedback sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis in posttraumatic stress disorder (PTSD) by using a low dose of dexamethasone.* *Method:* *Baseline blood samples were obtained at 8:00 a.m., and 0.5 mg of dexamethasone was administered to 21 male patients with PTSD and 12 normal age-comparable men at 11:00 p.m. Cortisol and dexamethasone levels were measured 9 and 17 hours after dexamethasone administration.* *Results:* *After correction for differences in dexamethasone levels, the PTSD patients showed greater suppression of cortisol in response to dexamethasone than did the normal subjects. This was true even in patients meeting concurrent diagnostic criteria for major depression.* *Conclusions:* *The data support earlier studies showing that HPA abnormalities in PTSD are different from those seen in depression and suggest that the low-dose dexamethasone suppression test may be a potentially useful tool for differentiating the two syndromes and further exploring differences in their pathophysiology.*
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There is considerable debate concerning the nature of hypothalamic-pituitary-adrenal (HPA) abnormalities in posttraumatic stress disorder (PTSD). Our work has provided evidence for lower than normal HPA activity, possibly secondary to enhanced negative glucocorticoid feedback sensitivity. We have reported both lower mean 24-hour urinary cortisol excretion (1, 2) and more lymphocyte glucocorticoid receptors (3) in patients with PTSD than in normal subjects. These findings are opposite of the hypercortisolemia reported in major depression.

In contrast to the aforementioned findings, others have suggested that the HPA axis may be overactivated in PTSD in a manner similar to that observed in depression. One study showed greater than normal urinary cortisol excretion (4), and another demonstrated blunted ACTH response to corticotropin-releasing factor (5). Data from dexamethasone suppression test (DST) studies of PTSD patients have been inconclusive in regard to abnormal cortisol metabolism in PTSD. Of the four published reports (6–9), all indicated normal suppression of cortisol in nondepressed PTSD patients given the standard DST. In PTSD patients meeting concurrent criteria for major depression, two studies (6, 7) showed a nonsuppressive response to dexamethasone in some patients, and two studies (8, 9) showed normal suppression in this subgroup.

To further explore HPA axis dysfunction in PTSD patients, we administered a low dose of dexamethasone to patients and normal subjects. Given the preliminary data from our laboratory suggesting the possibility of more effective feedback inhibition, we hypothesized that rather than showing the classic nonsuppression observed in many patients with major depression, PTSD patients would suppress cortisol to a greater extent than normal subjects in response to dexamethasone. If so, the standard 1-mg dose, which almost completely suppresses the normal cortisol response, would be too high to effectively discriminate normal from subnormal responses. In the present pilot study, 0.5 mg of dexamethasone, which produces more modest suppression in normal subjects, was used to explore the possibility of enhanced suppression of cortisol after dexamethasone administration in PTSD patients with and without comorbid major depression.

METHOD

The subjects were 21 nonmedicated male Vietnam combat veterans with PTSD (mean age=41.9 years, SD=2.4, range=38–48) and 12 normal age-comparable

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TABLE 1. Mean Cortisol and Dexamethasone Blood Levels After 11:00 p.m. Administration of 0.5 mg of Dexamethasone in Male Vietnam Veterans With PTSD and Age-Comparable Normal Men

	Cortisol (μg/dl)[a]						Dexamethasone (ng/ml)[b]			
	Baseline		8:00 a.m.		4:00 p.m.		8:00 a.m.		4:00 p.m.	
Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Normal (N=12)	15.09	4.17	4.78	2.93	4.51	2.28	1.46	0.48	0.53	0.28
PTSD (N=21)	14.29	3.70	1.78[c]	1.45	1.89[c]	1.36	2.19[c]	0.64	0.86[c]	0.32
With major depression (N=11)	14.14	4.02	2.07[c]	1.83	1.83[c]	1.26	2.35[c]	0.66	0.88[c]	0.33
Nondepressed (N=10)	14.49	3.39	1.41[c]	0.60	1.96[c]	1.57	1.98	0.64	0.84	0.34

[a]Means of cortisol values at 8:00 a.m. and 4:00 p.m. were 1.49 and 1.25 μg/dl, respectively.
[b]Means of dexamethasone values at 8:00 a.m. and 4:00 p.m. were 0.41 and 0.22 ng/ml, respectively.
[c]Significantly different from value for normal subjects ($p<0.05$, two-tailed, Tukey's honest significance difference test).

men (mean age=41.0 years, SD=6.2, range=30–49); all gave written informed consent. The patients were recruited from a specialized inpatient PTSD program at a U.S. Department of Veterans Affairs medical center. The normal subjects were largely hospital personnel, students, and acquaintances who responded to advertisements within the medical center. The normal subjects were screened for axis I disorders and for family history of psychiatric illness. All patients were free from psychoactive substance abuse, as confirmed by urine toxicology screens, for at least 1 month before testing. The patients were also free from major medical, endocrinological, psychotic, and organic illness as determined by history, physical examination, and routine clinical laboratory tests, including thyroid and liver function tests.

The patients were interviewed with the Structured Clinical Interview for DSM-III-R (SCID) (10). After diagnostic evaluation, the patients were further subdivided into those meeting and not meeting concurrent DSM-III-R criteria for major depression. Severity of PTSD was determined with the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder (11), and depressive symptoms were assessed by using the 21-item Hamilton Rating Scale for Depression (12).

Baseline blood samples were obtained at 8:00 a.m. on the morning of the DST. At 11:00 p.m. each subject received an oral dose of 0.5 mg of dexamethasone. Blood samples for determination of cortisol and dexamethasone levels were obtained at 8:00 a.m. and 4:00 p.m. the following day. Plasma cortisol levels were determined with a commercially available radioimmunoassay kit, as previously described (2, 3). The inter- and intra-assay coefficients of variation for this method in our laboratory are 6.8% and 4.0%, respectively. Dexamethasone levels were measured by radioimmunoassay using a commercially available antibody (IgG Corporation, Nashville, Tenn.), as previously described (13). This assay can sensitively quantify dexamethasone levels of 0.20 ng/ml. The inter- and intra-assay coefficients of variation for this procedure are 8.2% and 6.0%.

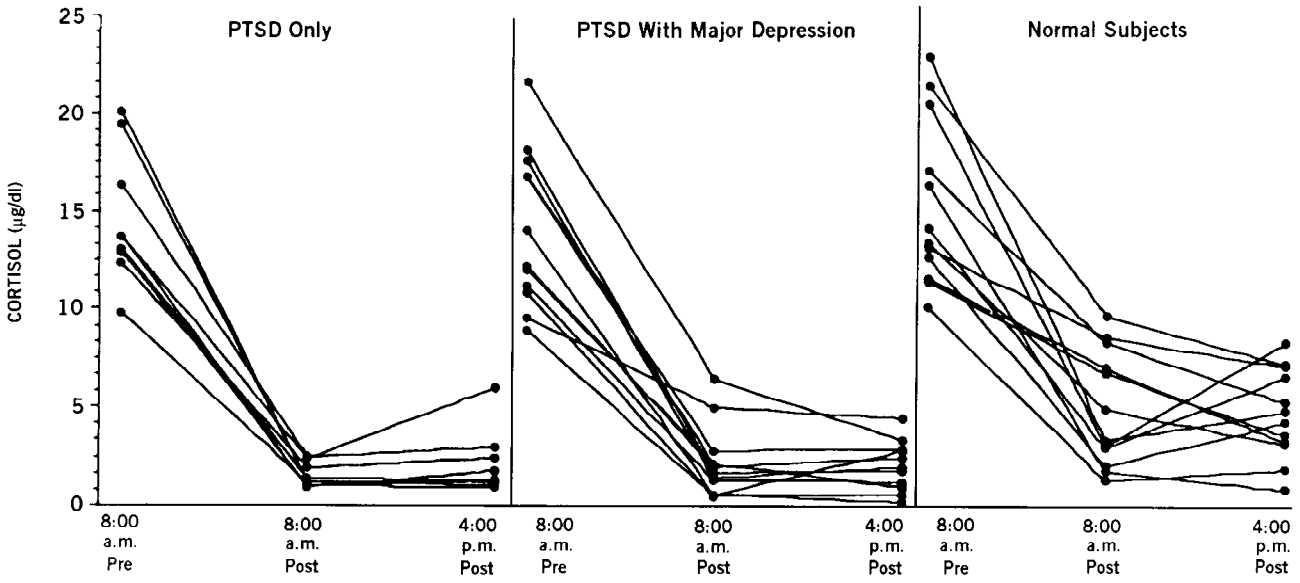
Because of an a priori assumption that PTSD patients would show lower than normal baseline cortisol levels, the data were subjected to two-way repeated measures multivariate analysis of covariance (MANCOVA) (Group by Time) with baseline cortisol levels used as covariates. For this analysis all PTSD patients were combined into one group and compared to the normal subjects. The dexamethasone data were analyzed by using a two-way repeated measures MANOVA (Group by Time). Because of group differences in dexamethasone levels, the cortisol data were reanalyzed by using the dexamethasone values at 8:00 a.m. and 4:00 p.m. as covariates to correct for differences in dexamethasone levels (13). Next, the PTSD patients were subdivided into those with and without major depression, and they were compared to the normal subjects by means of the aforementioned analyses. Post hoc testing was performed by using the Tukey's honest significance difference test (two-tailed), at an alpha level of $p<0.05$. Differences in clinical symptoms between the PTSD subgroups with and without major depression were evaluated by using Student's t test, two-tailed. Statistical analyses were performed on a microcomputer with SPSS (14).

RESULTS

Table 1 summarizes the biological data. In an initial analysis comparing the PTSD group as a whole to the normal subjects, MANCOVA revealed a significant group difference in the cortisol response to dexamethasone when the baseline cortisol values were used as covariates ($F=21.2$, $df=1, 30$, $p<0.0001$). Dexamethasone levels were also found to be significantly different in the two groups ($F=11.37$, $df=1, 31$, $p<0.002$). After correction of the cortisol data for differences in dexamethasone levels the PTSD patients still showed significantly greater cortisol suppression in response to 0.5 mg of dexamethasone ($F=9.01$, $df=1, 30$, $p<0.005$).

A secondary analysis was performed in which the PTSD patients were subdivided on the basis of the presence or absence of comorbid major depression. MANCOVA revealed an overall main effect of group in the cortisol response to dexamethasone ($F=10.39$, $df=2, 29$, $p<0.0001$), reflecting the fact that the cortisol response to dexamethasone in both PTSD subgroups differed from that of the normal subjects. However, post hoc testing revealed no significant differences in cortisol between the PTSD subgroups (table 1). In contrast, post hoc testing revealed that the significant main effect for

FIGURE 1. Individual Cortisol Blood Levels After 11:00 p.m. Administration of 0.5 mg of Dexamethasone in Male Vietnam Veterans With PTSD and Age-Comparable Normal Men



group (F=6.26, df=2, 30, p<0.005) in dexamethasone levels reflected a significantly higher drug level only in the PTSD patients with concurrent major depression. The dexamethasone levels of the PTSD patients without depression were comparable to those of the comparison subjects. When the cortisol data were again analyzed by using dexamethasone levels as covariates to control for differences in dexamethasone pharmacokinetics, MANCOVA revealed a significant main effect of group (F=4.9, df=2, 29, p<0.01). Post hoc testing revealed that the PTSD subgroups were comparable with respect to cortisol levels but that both groups' cortisol secretion was lower than that of the normal subjects (figure 1).

There were no significant correlations between liver enzymes and suppression of cortisol in the PTSD group (SGPT: r=0.06, df=18; alkaline phosphatase: r=0.05, df=18; LDH: r=0.06, df=17; SGOT: r=0.09, df=18).

There were no significant differences in severity of PTSD, as reflected by the Mississippi scale scores, between the PTSD patients with and without major depression (with depression: mean=134.7, SD=16.0; without depression: mean=130.0, SD=10.5). The Mississippi scale scores in both groups were in the severe range. There were also no significant differences in Hamilton depression scores between the two PTSD subgroups (with depression: mean=28.3, SD=7.2; without depression: mean=21.8, SD=12.6).

DISCUSSION

By using a low dose of dexamethasone it was possible to determine that rather than showing a normal or nonsuppression response to dexamethasone, as reported by other investigators (6–9), PTSD patients show an exaggerated suppression response to dexamethasone regardless of whether or not they concurrently meet diagnostic criteria for major depression. These results are consistent with our previous reports of low mean basal 24-hour urinary cortisol excretion (1, 2) and a higher than normal number of lymphocyte glucocorticoid receptors (3) in PTSD with and without major depression, and they support the developing hypothesis of an abnormally sensitive negative feedback system in the HPA axis (15).

Indeed, if the number of steroid receptors in the PTSD group were higher than in the normal subjects, as determined in the previous study, this would be consistent with the "supersuppression" in response to dexamethasone observed in the present study. A greater than normal availability of steroid receptors would theoretically allow for enhanced migration of the steroid receptor complex into the cell nucleus, where the steroid could exert genomic effects, resulting in a compensatory decrease in cortisol production. Basal and postdexamethasone glucocorticoid receptors are currently being measured in our laboratory to directly address this question.

An exaggerated cortisol response to dexamethasone could also occur in cases where dexamethasone bioavailability is greater than normal. In the present study PTSD patients showed a higher mean dexamethasone level than the normal subjects. However, the greater cortisol suppression in response to dexamethasone in the present study is not likely to have resulted solely from differences in dexamethasone levels because 1) correcting the cortisol data for differences in dexamethasone levels still resulted in significant group differences in postdexamethasone cortisol levels between the PTSD patients and normal subjects, and 2) dexamethasone levels were only significantly higher in the PTSD group with depression, whereas the two PTSD

subgroups showed comparable cortisol responses to dexamethasone and, in fact, the PTSD group without depression showed a slightly more dramatic response. Dose-response pharmacokinetic studies measuring dexamethasone levels at earlier time points after dexamethasone administration in a larger group of PTSD and normal subjects are clearly needed to further explore this issue.

Differences in dexamethasone bioavailability can result from a number of factors, including abnormalities in hepatic metabolism (13, 16) and medication effects (17). Specifically, in a study of patients with liver damage (16), the plasma half-life of dexamethasone was longer than normal. Given that most of the patients in the present study had histories of alcoholism, it is possible that long-term changes in hepatic function account for some of the present findings. Of note, Carson et al. (18) reported that recently detoxified alcoholics with abnormal liver function had lower postdexamethasone cortisol levels than did alcoholics with normal liver function. Although examination of the raw data revealed no obvious relationships between liver enzymes (SGOT, SGPT, LDH, and alkaline phosphatase) and cortisol suppression in the subjects in the present study, it is difficult to comment on the effect of liver function on DST results in the present study because the patients differed substantially on time since last drink, and liver function tests were performed anywhere from a week to a month before the DST. Medication effects on dexamethasone pharmacokinetics are unlikely, as all patients were medication free. Other factors that may account for differences in dexamethasone bioavailability, such as differences in the metabolism of dexamethasone by other tissue, such as lymphocyte and kidney (13), should be explored in subsequent studies. The present findings are consistent with reports of large interindividual differences in dexamethasone metabolism (13, 19) and support the use of indexes of dexamethasone bioavailability in studies of cortisol responsiveness to dexamethasone (19).

In the present study, the two PTSD subgroups were comparable with respect to severity of PTSD and severity of depression. That the PTSD patients with depression had Hamilton depression scores in the same range as those of the PTSD patients without depression underscores the observation that PTSD inpatients may be quite depressed regardless of whether they meet the full DSM-III-R criteria for major depression (20). Additionally, given the large symptom overlap between PTSD and depression (in symptoms of insomnia, impaired concentration, loss of interest, and social withdrawal), the high Hamilton scores in the PTSD patients may reflect severity of PTSD as well as depression. In any event, the lack of a significant difference in clinical symptoms between the two subgroups is consistent with the lack of difference in cortisol suppression after dexamethasone administration.

The present findings should be considered preliminary because of the small number of subjects; however, they may have important clinical implications. Many patients with PTSD also meet diagnostic criteria for major depression. However, it is presently unclear whether the frequent co-occurrence of depression represents a true melancholia or a different dysthymic disorder that may be unique to PTSD. The current data support the latter hypothesis. Thus, the low-dose DST may be a potentially useful clinical and experimental tool for teasing apart these two syndromes and for further exploring their distinct pathophysiologic abnormalities.

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